INTRODUCTION

Incretins, or gut hormones (glucagon-like peptide-1 = GLP-1, and glucose-dependent insulinotropic polypeptide = GIP), exert several beneficial effects in glycemic control, collectively called the "incretin effect". The "incretin effect" refers to the amplification of the insulin response to glucose, when delivered orally as opposed to intravenously (Perley et al. 1967). Studies in experimental animals have demonstrated that GLP-1 and GIP are needed for the maintenance of normal glucose tolerance (Scrocchi et al. 1996, Miyawaki et al. 1999). GIP is released into the circulation after ingestion of a meal; fat and carbohydrates seem to be predominant stimulators, whereas protein seems to be less important. The GLP-1, on the other hand, is released into circulation minutes after meal ingestion; fat, carbohydrates, and protein seem all to be powerful stimulators of GLP-1 secretion. Both GIP and GLP-1 are rapidly inactivated after their release. The inactivation is caused by a truncation of the peptides by removal of the N-terminal dipeptide end; such a process is executed by the enzyme DPP-4. Inhibition of DPP-4 by gliptin class (vildagliptin, sitagliptin, saxagliptin) substantially prolongs this half-life and increases the proportion of active GLP-1 in the total GLp-1 pool. In patients with type 2 diabetes mellitus (T2DM), secretion of GLP-1 is lower than normal and increasing GLP-1 decreases blood glucose, which suggest that this hormone may contribute to the pathogenesis of T2DM. The major therapeutic drawback to using native GLP-1 is its very short half life of less than 2 (two) minutes following exogenous administration, due to in part to the protease DPP-4 (Deacon et al. 1995). There are 2 (two) approaches to enhance endogenous GLP-1 action in vivo Incretin Mimetic (GLP-1 Analogues and Exenatide = Exendin-4) and DPP-4 inhibitors (Vildagliptin, Sitagliptin, Saxagliptin) which may increase the incretin hormones (GLP-1 and GIP) by inhibiting the enzyme responsible for their degradation (Deacon et al. 1995). On the basis of the data on efficacy, safety, and tolerability of vildagliptin either in monotherapy or in combination, in patients failing monotherapy on other T2DM treatments, it can be concluded that vildagliptin 50 mg once daily and twice daily, and 100 mg once daily show: 1. promising regimen that can be used as a novel strategy for the treatment of T2DM; 2. therapeutic value if in combination with metformin, glitazone, and other commonly used OADs; 3. beneficial effects in diabetic insulin-treated patients with inadequate glycemic control.

Keywords: Incretins, GIP, GLP-1, T2DM, Vidalagptin

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function (Duttory et al. 2005, Mari et al. 2005), and improvement of myocardial and endothelial function (Henness et al. 2006).

The GIP is produced mainly by the K-cells, which are located predominantly in the duodenum. GIP is released into the circulation after ingestion of a meal; fat and carbohydrates seem to be predominant stimulators, whereas protein seems to be less important. The GLP-1, on the other hand, is produced by the L-cells, which are localized predominantly in the distal ileum and colon. GLP-1 is released into circulation minutes after meal ingestion; fat, carbohydrates, and protein seem all to be powerful stimulators of GLP-1 secretion.

Both GIP and GLP-1 are rapidly inactivated after their release. The inactivation is caused by a truncation of the peptides by removal of the N-terminal dipeptide end; such a process is executed by the enzyme DPP-4. This truncating effect of DPP-4 is rapid and efficient; only 40% of total GLP-1 in the circulation under fasting conditions (and 60% after meal ingestion) is active GLP-1, and the half life of GLP-1 is less than 2 (two) minutes. Inhibition of DPP-4 by gliptin class (vildagliptin, sitagliptin, saxagliptin) substantially prolongs this half-life and increases the proportion of active GLP-1 in the total GLP-1 pool.

Besides the incretin hormones, a number of other bioactive peptides are potential substrates for DPP-4, e.g.: neuropeptidyl Y, peptide YY, gastrin-releasing polypeptide, IGF-1, substance P, and various chemokines may be mentioned by DPP-4. Hence, DPP-4 is involved not only in glucose homeostasis but also in the regulation of other homeostatic mechanisms, such as blood pressure, neurogenic inflammation, and the immune system. However, such potential action of DPP-4 does not seem to be affected by DPP-4 inhibitors.

Dipeptidyl Peptidase-4 (DPP-4, DPP IV, CD 26, EC 3.4.14.5) was first described in 1996 as an enzyme occurring in homogenates of rat livers, that is widely distributed in numerous tissue and T-cell, B-cell, and natural killer cells. DPP-4 belongs to a family of enzymes. Inhibiting the other enzymes in this family may cause adverse events, as has been demonstrated in animal studies showing toxicity after inhibition of DPP-8 and DPP-9. Both vildagliptin and sitagliptin show selectivity for DPP-4 over other enzymes within this family. Both vildagliptin and sitagliptin are orally active and rapidly absorbed; C max is observed within 1-2 hours, and bioavailability exceeds 80% after oral intake.

Hepatic insufficiency does not seem to alter the pharmacokinetics of the compounds, but renal insufficiency increases circulating levels of sitagliptin. The FDA has therefore recommended that renal function is assessed prior to the start of sitagliptin treatment, and that inpatients moderate (creatinine clearance <50 ml/min) or severe renal insufficiency (creatinine clearance <30 ml/min) the dose of sitagliptin should be reduced to 50 and 25mg, respectively. Furthermore, the FDA has asked Novartis to conduct an additional study to demonstrate the safety of vildagliptin in patients with renal impairment.

Most evidence favors the opinion that the beneficial effects of DPP-4 inhibitors are mediated largely by GLP-1. DPP-4 inhibition really increases concentrations of active GLP-1 after meal ingestion (Ahrén et al. 2004). It has been shown that not only the prandial GLP-1 levels are elevated by DPP-4 inhibition, but also the entire 24-hour pattern of GLP-1 levels is increased, including fasting levels, and at the same time a circadian rhythm with clear increases after meal can be seen (Mari et al. 2005).

Vildagliptin (Galvus®) is a competitive and reversible inhibitor of DPP-4 which acts mainly by preventing the rapid degradation of GLP-1 by DPP-4. Vildagliptin shows considerable promise as combination therapy with metformin, glitazones, other commonly used oral agents for diabetes (OADs), and also may play an important role in combination with insulin to further improve glycemic control for patients with diabetes or even for prediabetes. Consistent with the importance of glucagon suppression and reduction of gastric emptying by GLP-1 action, short-term studies demonstrated that GLP-1 significantly lowers blood glucose in patients with type 1 diabetes mellitus = T1DM (Guttiak et al. 1992, Dupre et al. 1995).

**DIABETES AND DPP-4 INHIBITORS**

In patients with type 2 diabetes mellitus (T2DM), secretion of GLP-1 is lower than normal and increasing GLP-1 decreases blood glucose, which suggest that this hormone may contribute to the pathogenesis of T2DM. The major therapeutic drawback to using native GLP-1 is its very short half-life of less than 2 (two) minutes following exogenous administration, due to in part to the protease DPP-4 (Deacon et al. 1995). There are 2 (two) approaches to enhance endogenous GLP-1 action in vivo (TABLE-1): Incretin Mimetic (GLP-1 Analogues and Exenatide = Exendin-4) and DPP-4 inhibitors (Vildagliptin, Sitagliptin, Saxagliptin) which may increase the incretin hormones (GLP-1 and GIP) by inhibiting the enzyme responsible for their degradation (Deacon et al. 1995).

Although non pharmacological therapy (e.g., lifestyle modifications: diet, exercise, and weight loss) remains a
critical component in the treatment of diabetes, pharmacologic therapy is often necessary to achieve optimal glycemic control. Orally administered antihyperglycemic agents can be used either alone or in combination with other OADs or insulin. The number of available OADs has increased significantly in the last decade, which translates into more therapeutic options and complex decision-making. The forthcoming novel OADs of other specific types of DPP-IV inhibitor group like vildagliptin and sitagliptin have been available in Indonesia.

Besides, metformin has also effects as an inhibitor of DPP-IV or stimulator of GLP-1 synthesis, which may result in increased GLP-1 levels. Several practice points have been suggested by Ahren (2007): DPP-4 inhibitors are orally active, safe and highly tolerable. They improve glycemic control both in monotherapy and in combination with metformin and thiazolidinediones, and they may also become candidates for first-line treatment, particularly in combination with metformin. To date, seven OADs mentioned below have claimed to have atheroprotective properties (Tjokroprawiro 2005, 2006): Glimepiride, Gliclazide, Metformin, Thiazolidinediones, Meglitinides (replaglinide, nateglinide), Acarbose, and Fixed Dose Combination (FDC) drugs: glucovance, avandamet, avandaryl, amaryl-M.

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**TABLE–1 Map of Oral Antidiabetic Drugs in Daily Practice**

(Summarized : Tjokroprawiro 1996 – 2008)

<table>
<thead>
<tr>
<th>1</th>
<th>INSULIN SECRETAGOGUES : SULPHONYLUREAS = SU₉</th>
<th>NON-SU₉ : Meglitinides (Nateglinide, Repaglinide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>INSULIN SENSITIZERS AND ANTIHYPERGLYCEMIC AGENTS :</td>
<td></td>
</tr>
<tr>
<td>Gen I :</td>
<td>Tolbutamide, Chlorpropamide, etc.</td>
<td></td>
</tr>
<tr>
<td>Gen II :</td>
<td>Glipizide-GITS, Gliquidone, Gliclazide - MR</td>
<td></td>
</tr>
<tr>
<td>Gen III : Glimipiride</td>
<td>No Effects at CV Kᵢᵣ, 3B-3A-9D Properties, Insulin Sparing, Glycogenic, Antiplatelet, Adiponectin-Raiser</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>INTOESTINAL ENZYME INHIBITORS :</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>α-GLUCOSIDASE INHIBITORS : Acarbose, Voglibose (AD-128), Miglitol, MDL-73945, Castanospermine</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>α-AMYLASE INHIBITOR : Tendamistase</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>FIXED DOSE COMBINATION TYPES :</td>
<td>Glucovance®, Avandamet®, Avandaryl®, Amaryl-M®</td>
</tr>
<tr>
<td>5</td>
<td>OTHER SPECIFIC TYPES :</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Insulin Mimetic Drugs (GLIMEPIRIDE, Chromium, α-Lipoic Acid, Vanadium)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Inhibitors of Dipeptidyl Peptidase-IV (DPP-IV – Inhibitors) : Metformin, Vildagliptin, Sitagliptin, Saxagliptin</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Suppresors of Glucagon Secretion: Amylin Analogues e.g Pramlintide</td>
<td></td>
</tr>
</tbody>
</table>

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**THE POTENTIAL ADVANTAGES OF VILDAGLIPTIN (GALVUS®)**

While the DPP-4 inhibitors (f.e vildagliptin) do not lower glucose to a greater extent than previous exiting therapies (f.e the former therapies with metformin, glitazones, OAD or insulin), due to its pleiotropic actions, the author summarized Barnett’s clinical review the 10 (ten) potential advantages of vildagliptin. Vildagliptin shows the ability to achieve sustainable reductions in A1C, it is well tolerated agent, has low risk of hypoglycemia, has weight neutrality, can be administered as a once daily oral dose, can preserve and reversal of the progressive loss of insulin secretory capability of patients with T2DM, theoretically, vildagliptin can be started soon for prediabetes, or after diagnosis of T2DM, before β-cell function has deteriorated to unacceptable levels, can be used as combination therapy with metformin, glitazones, the commonly use OADs, acarbose, and insulin, can be prescribed for patients with T1DM due to its suppression of glucagon and its effects in slowing gastric emptying, and Vildagliptin improves β-cell mass and β-cell function.
Vildagliptin monotherapy trials in T2DM, in all trials, elderly patients (Rosenstock et al. 2008). In patients with T2DM, vildagliptin 50 mg once daily and twice daily, and 100 mg once daily have been assessed in placebo-controlled and, more importantly, in-head-to-head active comparator monotherapy trials over a wide range of baseline A1C levels and in a large number of elderly patients (Rosenstock et al. 2008).

Vildagliptin monotherapy trials in T2DM, in all trials, vildagliptin was weight neutral, and posed minimal risk of hypoglycemia, in dose ranging study, its efficacy over 24-weeks with once-or twice-daily dosing. Vildagliptin and Rosiglitazone has similar efficacy at 24 weeks. Vildagliptin vs Pioglitazone as add-on to pioglitazone. In a 24 week study in 465 patients with suboptimal control on glimepiride 4 mg / day resulted in a significant –0.6% decrease in A1C from baseline (~ 8.5%) compared with ongoing glimepiride plus placebo

Pooled monotherapy (in phase III: placebo-or active comparator –controlled) with vildagliptin 100 mg daily in drug-naïve patients (n = 1469) proceed an adjusted mean change in A1C of –1.0% at 24 weeks from a baseline of 8.6%, including reductions of 1.1% in those receiving 100mg once daily and 1.0% in those receiving 50% twice daily. Rosenstock et al. 2008 concluded that pooled monotherapy trial data with vildagliptin is efficacy, safety, and tolerability.

Vildagliptin in Impaired Glucose Tolerance (IGT). In a proof of concept trial, patients with IGT (by OGTT) were randomized in double blind fashion to vildagliptin 50mg once daily (n = 90) or placebo (n = 89) for 12 weeks (Rosenstock et al. 2008). Vildagliptin increased the prandial GLP-1 level, suppressed glucagon production, improved β-cell function and reduced prandial glucose excursions compared with placebo. Overall, vildagliptin reduced glycemic excursions by 22% compared to baseline, and by 32% compared by placebo in post-treatment testing. Thus, the vildagliptin regimen was very well tolerated in IGT subjects, and no hypoglycemia was reported.

Vildagliptin Combination Therapy Trial in T2DM. Vildagliptin (50mg twice daily) as add-on to metformin (> 1.500 mg/daily), 50 mg twice daily plus metformin was body weight neutral, vildagliptin patients having an insignificant mean change of + 0.2 kg in weight over 24 weeks. Vildagliptin vs Pioglitazone as add-on to Metformin. Pioglitazone treatment was associated with significantly greater body weight gain in all patients and in patients with baseline BMI >35 kg/m². Vildagliptin as add-on to pioglitazone, in a 24 week study in 465 patients with inadequate glycemic control (baseline A1C of ~ 8.7%) on pioglitazone monotherapy, addition of vildagliptin 50 mg once daily or 50 mg twice daily produced a significant A1C reduction from baseline of –0.8% and –1.0%, respectively, compared with –0.3% in those receiving placebo plus pioglitazone (Gurber et al. 2007). Vildagliptin as add-on to Glimipiride. The addition of vildagliptin 50 mg once daily to 408 diabetic patients with suboptimal control on glimepiride 4 mg / day resulted in a significant –0.6% decrease in A1C from baseline (~ 8.5%) compared with ongoing glimepiride plus placebo

Combination Vildagliptin plus Pioglitazone as Initial Therapy. This 12 week study assessed the effects of vildagliptin 100 mg once daily, pioglitazone 30 mg once daily, and vildagliptin combined with pioglitazone 50/15 mg or 100/30 mg once daily in drug-naïve T2DM with a baseline A1C of ~ 8.7%)

Results of A1C reductions from baseline :
Vildagliptin monotherapy 100 mg once daily: –1.1%; Pioglitazone monotherapy 30 mg once daily: –1.4%; Combination 50/15 mg: –1.7%; Combination 100/30 mg: –1.9%.

Results of A1C target <7% (% achievement of patients): 65% of patients in the combination vildagliptin – pioglitazone 100/30 mg; 43% of patients in the vildagliptin monotherapy; 43% of patients in the pioglitazone monotherapy.

Weight gain in the combination 100/30 group is most likely reflected the effect from the pioglitazone component (+2.1 kg) as it was not significantly different from that seen in the pioglitazone monotherapy group. Peripheral oedema occurred in 9.3% of patients receiving pioglitazone monotherapy and 3.5% in those receiving the low-dose combination (Rosenstock et al. 2008).

Vildagliptin as add-on to Insulin. In a randomized, double blind trial, patients with inadequate glycemic control on insulin therapy (A1C of 7.5-11.0%,mean baseline 8.4%) received vildagliptin 50mg twice daily (n = 144) or placebo (n = 152) for 24 weeks (Fonseca et al. 2007), and insulin doses were kept constant during the study, although investigator adjustments of dose were permitted.

Results: Insulin dose increased only by 1.2U/day in vildagliptin patients, and by 4.1U/day in placebo patients; at 24 weeks, A1C was reduced by 0.5% with vildagliptin, compared with 0.2% with placebo (p = 0.01); in subgroup of patients aged > 65 years, vildagliptin significantly reduced A1C by 0.7% compared with 0.1% for placebo (p = 0.001); overall, 113 hyperglycemic events occurred in 33 patients in the
vildagliptin group, and 185 events occurred in 45 patients in the placebo (a significant 40% reduction in the number of hypoglycemic events). This finding raises the potential benefit of vildagliptin to protect against insulin-related hypoglycemia for insulin-treated diabetic patients.

On the basis of the data on efficacy, safety, and tolerability of vildagliptin either in monotherapy or in combination, in patients failing monotherapy on other T2DM treatments, it can be concluded that vildagliptin 50 mg once daily and twice daily, and 100 mg once daily show: 1. promising regimen that can be used as a novel strategy for the treatment of T2DM; 2. therapeutic value if in combination with metformin, glitazone, and other commonly used OADs; 3. beneficial effects in diabetic insulin-treated patients with inadequate glycemic control. In patients with stable insulin therapy, vildagliptin 50 mg twice daily improved glycemic control and was associated with a significant reduction in hypoglycemic episodes over 24 weeks.

**PUBLISHED PHASE 2 AND PHASE 3 CLINICAL TRIAL DATA FOR VILDAGLIPTIN**

Summarized article reviews of Barnett (2006) contained phase 2 and phase 3 clinical trial data for vildagliptin which can be seen in TABLE-2. Five clinical trials (4-52 weeks study period) have shown the efficacy of vildagliptin as monotherapy on markers of glycaemic control in drug-naïve patients compared with placebo and head-to-head trials with commonly prescribed OADs. The results of phase 2 and phase 3 clinical trial for vildagliptin are summarized below (Barnett 2006).

### Table 2. Comparison of Published Phase 2 and Phase 3 Clinical Trial Data for Vildagliptin (Barnett 2006, Summarized 2008)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study duration weeks</th>
<th>Sample: PCB = Placebo Treatment</th>
<th>Findings between group difference in adjusted mean change Glycemic control</th>
<th>Hypoglycemic events</th>
<th>Weight changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy Ahrén et al (2004)</td>
<td>4</td>
<td>Treatment naïve Mean age 65 year BMI 27.3kg/m² Baseline A1C 7.2% (6.3%-10%) Baseline FPG 8.8 (7.2 10.0mmol/l)</td>
<td>Vildagliptin 100mg time/day (n=18) vs PCB 9 (n=19)</td>
<td>FPG-0.7 (p=0.037) 4-h PPG-1.45 (p=0.0001)</td>
<td>None 0.21 kg Vildagliptin 0.12 kg PCB P = ns</td>
</tr>
<tr>
<td>Ristic et al (2005)</td>
<td>12</td>
<td>Mean age 51-63 years BMI 30.9-31.6 kg/m² Baseline A1C 7.6-7.8 Baseline FPG 9.2-9.4 Diabetes duration 2.3-3.3 year</td>
<td>Vildagliptin 25 mg 2 times/day, 25,50 or 100mg 1 time/day, PCB (n=279)</td>
<td>A1C -0.31% (Vildagliptin 25 mg 2 times/day) to 0.56% (Vildagliptin 50 mg 1 time/day) vs -0.13% (PCB) FPG-0.44 (Vildagliptin 25 mg 2 times/day) to 0.97 (Vildagliptin 50 mg 1 time/day) vs -0.41(PCB)</td>
<td>Two cases of symptomatic confirmed hypoglycaemia (Vildagliptin 25 mg 2 times/day and 100 mg 1 time/day) Small changes not significantly different from PCB</td>
</tr>
<tr>
<td>Pratley et al (2006)</td>
<td>12</td>
<td>Treatment naïve Mean age 54 years BMI 30.0 kg/m² Baseline A1C 8 (vildagliptin) 8.1 (PCB) Baseline FPG 9.4 (vildagliptin), 10.1 (PCB) Diabetes duration 3.5-4.6 years</td>
<td>Vildagliptin 25 mg 2 times/day (n=70) vs. PCB (n=279)</td>
<td>A1C -0.6% (p=0.0012) FPG-1.1 (p=0.0043) 4-h PPG-1.9 (p=0.0001)</td>
<td>One episode of symptomatic hypoglycaemia with Vildagliptin Small changes not significantly different from PCB</td>
</tr>
<tr>
<td>Rosenstock et al (2006)</td>
<td>24</td>
<td>Treatment naïve Mean age 54 years BMI 32.4 kg/m² Baseline A1C 8.7% Diabetes duration 2.4 years</td>
<td>Vildagliptin 50 mg 2 times/day (n=459) vs. Rosiglitazone 8 mg / day (n=238)</td>
<td>A1C -1.1% (Vildagliptin), non-inferior to Rosiglitazone</td>
<td>One mild hypoglycaemic event in each group -0.3 kg Vildagliptin + 1.6 kg Rosiglitazone (p=0.001)</td>
</tr>
<tr>
<td>DeJager et al (2006)</td>
<td>52</td>
<td>Treatment naïve Mean age 53.4 years BMI 32.4 kg/m² Baseline A1C 8.7% (7.5%-11%) Diabetes duration 2.4 years</td>
<td>Vildagliptin 50 mg 2 times/day (n=526) vs. Metformin 1000 mg 2 times/day (n=254)</td>
<td>A1C -1.1% (Vildagliptin) A1C -1.4% (Metformin)</td>
<td>Three (0.6%) Vildagliptin-treated patients reported one (0.4%) Metformin patient +0.3 kg Vildagliptin -1.9 kg Metformin</td>
</tr>
</tbody>
</table>
In a 4-week study 1. 100 mg vildagliptin/day vs placebo (baseline A1C 7.2%, FPG 8.8 mmol/l). 2. FPG was reduced by 0.7 mmol/l; 3. Prandial plasma glucose by 1.45 mmol/l; 4. Mean 24h glucose by 0.93 mmol/l compared with placebo. In a 12-week study designed to establish the dose of vildagliptin that was effective in reducing A1C levels and showed safety and tolerability in patients with T2DM (baseline A1C 7.6 – 7.8%, FPG 9.2–9.4 mmol/l for vildagliptin vs placebo, respectively. In a 24-week study of vildagliptin 50 mg b.i.d vs rosiglitazone 8 mg OD (base line A1C 8.7%) the adjusted mean change in A1C from baseline to endpoint in patients receiving vildagliptin was −1.1% and non-inferiority to rosiglitazone was established. In patients with baseline A1C > 9.0%, the mean change in A1C was −1.8% in the vildagliptin treated group and −1.9% in the rosiglitazone one.

In large 52-week study of vildagliptin 50 mg bid vs metformin 1.000 mg bid (baseline A1C 8.7%) showed an adjusted mean change in A1C from baseline to end of −1.0% for vildagliptin and −1.4% for metformin. While the between group difference in A1C did not established non-inferiority of vildagliptin 100 mg/day to metformin 2,000 mg/day, a clinically meaningful decrease in A1C was sustained throughout 1-year of treatment.

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